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09/545,428	04/07/2000	Michel F Levesque M D	CEDAR-044526	1086

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EXAMINER	
LACOURCIERE, KAREN A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 02/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/545,428	LEVESQUE M D ET AL.	
	Examiner	Art Unit	
	Karen A. Lacourciere	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,8,11,12,16 and 22-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,8,11,12,16 and 22-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a)☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Drawings

The corrected or substitute drawings were received on November 6, 2003.

These drawings are acceptable.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 5, 8, 11, 12, 16, and 22-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, 5, 8, 11, 12, 16, and 22-46 are indefinite due to the recitation of antisense "corresponding to" a human MSX1 or human HES1 gene. It is unclear what the meets and bounds of "corresponding to" are, with respect to an antisense molecule, for example, it cannot be determined what limiting physical characteristics of such an antisense are. Therefore, the characteristics of the antisense used in the claimed methods cannot be determined and the meets and bounds of the claimed methods and compositions cannot be determined.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 5, 8, 11, 12, 16, and 22-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 1, 2, 5, 8, 11, 12, 16, and 22-46 each include the limitation wherein the basal epidermal cells are "primary" basal epidermal cells. Applicant has not pointed to any support for this newly added limitation and no support for this limitation could be found in the originally filed specification or claims. It is noted that Applicant incorporated this limitation in response to the rejection of record under 35 USC 112, first paragraph, lack of enablement over the full scope claimed, set forth by the previous Examiner in the prior Office action, however, it is unclear that this was actually a suggested amendment by the Examiner, but rather the Examiner appears to have simply used her own term to describe the type of cells used in the examples of the specification. As such, the term "primary" is considered to be new matter.

Claims 1, 2, 5, 8, 11,12, 16 and 22-27 are maintained as rejected and new claims 28-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 1, 2, 5, 8, 11,12, 16 and 22-40 are drawn to methods that include the use of an expressed cDNA of any "homologous non-human counterpart" of the neurogeneic transcription factors NeuroD1, NeuroD2, ASH1, Zic1, Zic3 or MyT1, kits comprising these cDNAs or cells produced using these cDNAs. Claims 1, 2, 5, 8, 11,12, 16 and 22-27 are further drawn to methods that include the use of antisense corresponding to any "homologous non-human counterpart" of MSX1 or HES1.

For antisense sequences, the specification teaches on pages 13-14 the antisense to human MSX1 of SEQ ID NOS: 13 and 14 and the antisense to human HES1 of SEQ ID NOS:15 and 16. The GenBank Accession numbers are taught on page 14 for the human, *Ambystoma mexicanum* and chicken MSX1 gene and the human, rat, mouse, newt, yeast (*Saccharomyces pombe* and *Saccharomyces cerevisiae*) genes.

For neurogenic transcription factors, the specification teaches the sequences of human NeuroD1, NeuroD2, ASH1, Zic1, Zic3 and MyT1 (by reference to Genbank accession numbers) and indicates that homologous sequences are available through Genbank. A search of Genbank, however, indicates that only a few species of each of these factors is known. Many of the homologus sequences listed in Genbank are actually partial sequences, with some sequence similarity, but without any characterized activity.

The scope of the claimed invention encompasses antisense compounds corresponding to a very broad genus of MSX1 genes and HES1 genes that are not

properly described in the specification as filed, nor were they described by the art at the time of filing. Additionally, the scope of the claimed invention encompasses cDNAs of a very broad genus of neurogenic transcription factors NeuroD1, NeuroD2, ASH1, Zic1, Zic3 and MyT1 which were not properly described by the specification or the art at the time the instant application was filed.

The sequences described in the specification for antisense corresponding to human HES1 or MSX1 and the cDNA's of the human neurogeneic transcription factors NeuroD1, NeuroD2, ASH1, Zic1, Zic3 and MyT1, do not provide the common structural features and

See the January 5, 2001 (Vol. 66, No. 4, pages 1099-1111) Federal Register for the Guidelines for Examination of Patent Applications Under the 35 USC §112 ¶1, "Written Description" Requirement. These guidelines state that: "To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the

claimed invention."

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of antisense compounds corresponding to the human MSX1 or HES1, or antisense corresponding to the limited number of homologues disclosed in Genbank at the time of filing, and the human neurogenic transcription factors NeuroD1, NeuroD2, ASH1, Zic1, Zic3 and MyT1 and the limited number of homologues provided in Genbank at the time of filing, the skilled artisan cannot envision the detailed chemical structure of the encompassed antisense compounds and neurogenic transcription factors, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

While the specification as filed teaches the Genbank sequences of human and other MSX1 and HES1 genes and neurogenic transcription factors NeuroD1, NeuroD2, ASH1, Zic1, Zic3 and MyT1 as summarized above, this teaching is not considered sufficient to describe the claimed genus of any non-human homologous counterpart as claimed, as the genus is highly variant. The examples in the specification are not considered representative of antisense to any MSX1 or HES1 gene from any species or neurogenic transcription factors NeuroD1, NeuroD2, ASH1, Zic1, Zic3 and MyT1 from any species since the examples in the specification are drawn only to human genes. Furthermore, it is not clear how antisense to any non-human homologous counterpart of MSX1 or HES1 and neurogenic transcription factors NeuroD1, NeuroD2, ASH1, Zic1, Zic3 and MyT1 would have a correlated function to allow for transdifferentiation of any type of epidermal basal cell into a cell expressing GFAP and/or O4. Absent further specific guidance by way of sequence structure, one of skill in the art would not have recognized that applicant was in possession of a representative number of species of the breath of claimed MSX1 and/or HES1 genes from the genus of species claimed.

Applicant's specification does not provide antisense compounds that correspond to a sufficient number of representative species of the genus HES1 and MSX1 and neurogenic transcription factors NeuroD1, NeuroD2, ASH1, Zic1, Zic3 and MyT1 which would allow one of skill in the art to predict the structures of all members of the claimed genus of antisense corresponding to any non-human homologous counterpart or cDNA of any non-human homologous counterpart. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Therefore, the specification does not describe the nucleic acids used in the claimed methods, used to make the claimed cell lines, or as part of the claimed kit, in such full and concise terms so as to indicate that the applicant had

possession of these compounds at the time of filing of this application. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Response to Arguments

Applicant's arguments filed 11-06-2003 have been fully considered but they are not persuasive. In response to the rejection of record under 35 USC 112 , first parargraph, as lacking adequate written description, Applicant argues that the specification describes using antisense corresponding to genes other than human genes and that the specification has disclosed Genbank numbers for other sequences by which the skilled artisan could use alignment and search tools to determine antisense sequences and by which the conserved regions of HES1 and MSX1 would become readily apparent to the skilled artisan.

This is not found to be persuasive, because only a very small number of species of HES1 and MSX1 genes were available in Genbank at the time of filing. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The small number of species disclosed in the specification and available in Genbank is not representative of the broad genus required by the claims. Although the skilled artisan may undergo further experimentation to find other members of the genus of sequences required by the claims, this would not support that the inventor was in possession of such sequences, or the full breadth of the claims, at the time of filing.

Claims 1, 2, 5, 8, 11, 12, 16 and 22-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claim 1 is drawn to an *in vitro* method of transdifferentiating an epidermal basal cell into a cell having one or more morphological, physiological and/or immunological feature(s) of a glial cell comprising:

a) culturing a proliferating epidermal basal cell population comprising one or more epidermal basal cell(s), said cell(s) derived from the skin of a mammalian subject;

b) transferring said epidermal basal cell, in vitro, with one or more eukaryotic expression vector(s) containing at least one cDNA encoding a human neurogenic transcription factor, or homologous non-human counterpart, selected from the group consisting of NeuroD1, NeuroD2, ASH1, Zic1, Zic3, and MyT1, such that at least one of the neurogenic transcription factor(s) is expressed in said cell;

c) growing the transfected cell in the presence of at least one antisense oligonucleotide comprising a segment of a human MSX1 gene and/or human HES1 gene, or homologous non-human counterpart of either of these, in an amount sufficient

to suppress the expression of functional MSX1 gene product and/or HES1 gene product;

d) growing said epidermal cell with a retinoid and at least one signal molecule selected from the group consisting of CNTF, sonic hedgehog, sonic hedgehog aminoterminal peptide, and IK-6, whereby the cell is transdifferentiated into a cell having one or more morphological, physiological and/or immunological feature(s) of a glial cell; and

wherein the physiological and/or immunological feature is expression of a marker selected from the group consisting of glial fibrillary acidic protein, and O4, or a combination of these.

Claim 2 is drawn to the method of claim 1, wherein the eukaryotic expression vector(s) of the transfection step comprise a CMV promoter sequence operatively linked to a DNA(s) encoding the neurogenic transcription factor selected from the group consisting of NeuroD1, NeuroD2, ASH1, Zic1, Zic3, and MyT1, and wherein the DNA encoding the neurogenic transcription factor is of human origin or is a homologous non-human counterpart.

Claim 5 is drawn to a trandifferentiated cell having one or more morphological, physiological and/or immunological feature(s) of a glial cell comprising:

an epidermal basal cell transfected with one or more eukaryotic expression vectors comprising a CMV promoter sequence operatively linked to a DNA(s) encoding the neurogenic transcription factor, or homologous non-human counterpart, selected from the group consisting of NeuroD1, NeuroD2, ASH1, Zic1, Zic3, and MyT1, wherein the DNA encoding the neurogenic transcription factor is of human origin, or is a non-human homologous counterpart, or is an active fragment of a gene encoding any of these, said cell being treated with at least one antisense oligonucleotide comprising a

segment(s) of human MSX1 gene or human HES1 gene, or non-human homologous counterpart thereof, and wherein said cell was grown in the presence of a retinoid and at least one signal molecule selected from the group consisting of CNTF, IL-6, sonic hedgehog, and sonic hedgehog aminoterminal peptide, thereby transdifferentiating said epidermal basal cell into a cell having one or more morphological, physiological and/or immunological feature(s) of a glial cell said cell expressing at least one marker selected from the group consisting of glial fibrillary acidic protein (GFAP) and O4, or a combination of these.

Claim 8 is drawn to a transdifferentiated cell produced by the process of claim 1.

Claim 11 is drawn to a kit for converting, in vitro, epidermal basal cells into cells having one or more morphological, physiological and/or immunological feature(S) of a glial cell, said kit comprising:

one or more eukaryotic expression vectors containing cDNA encoding a human neurogenic transcription factor, from the group consisting of NeuroD1, NeuroD2, ASH1, Zic1, Zic3, and MyT1, or a non-human homologous counterpart of any of these;

at least one antisense oligonucleotide corresponding to the human MSX1 gene, the human HES1 gene, or a non-human homologous \ counterpart of either of these,

and a retinoid and at least one signal molecule selected from the group consisting of CNTF, sonic hedgehog, and sonic hedgehog aminoterminal peptide.

Claim 12 is drawn to the kit of claim 11 further comprising instructions for using (a), (b), and c) in transdifferentiating a mammalian subject's epidermal basal cell(s).

Claim 16 is drawn to the transdifferentiated cell of claim 8, wherein the cell further displays the physiological feature of a lack of mitotic activity under cell culture conditions which induce differentiation in neural progenitor cells.

Claim 22 is drawn to the transdifferentiated cell of claim 8 wherein the cell is of human origin.

Claim 23 is drawn to the cell of claim 8, wherein the transdifferentiated cell has a morphological, physiological, or immunological feature specific to an astroglial or oligodendroglial cell.

Claim 24 is drawn to the transdifferentiated cell of claim 23, wherein the physiological and/or immunological feature is expression of glial fibrillary acidic protein (GFAP) or O4.

Claim 25 is drawn to an in vitro cell culture derived from the transdifferentiated cell of claim 8, comprising a plurality of cells that express one or more morphological, physiological and/or immunological feature(s) of a glial cell.

Claim 26 is drawn to the method of claim 1, wherein culturing a proliferating epidermal basal cell population comprising one or more epidermal basal cell(s) comprises separating basal cells from keratinocytes using a calcium-free medium.

Claim 27 is drawn to the method of claim 1, wherein said antisense oligonucleotide(s) is modified with one or more thio groups.

New claims 28-46 are drawn to methods, kits, and cells with the same limitations, however, the scope of these claims is narrower, excluding homologous antisense sequences (claims 28-40) and homologous transcription factors (claims 41-46).

The specification as filed teaches that human adult skin was cultured in calcium depleted media, basal cells were separated from keratinocytes and transfected with various combinations of the specifically claimed embodiments, including pRcCMVneo vectors containing B-gal, NeuroD1, NeuroD2, hASH1, Zic1 or hMyT1 human genes and antisense targeted to human MSX1 or HES1. The specification teaches that various methods can be used for detection of transdifferentiation of the epidermal cells to neural

cells including immunohistochemical detection of neurofilament M, neural specific tubulin, neural specific enolase, microtubule associated protein 2, neurofilaments Mix, filial fibrillary acidic protein, and morphological criteria including cells with neurites longer than three cell diameters (50 microns or longer).

Table 1 presents the results of the transdifferentiation experiments, wherein the cells resulting from transformation of basal epidermal cells with various combinations of antisense and/or neurogenic transcription factors are assessed for neuronal cell features. It is not entirely clear from the specification what neuronal features are required in Table 1 to be labeled as neuronal, but it appears from the column label that the cells were considered neuronal if they were positive for expression of Neurofilament M. (as it states " i.e. % Neurofilament M expressing"), although at other points the specification also states cells with neurites longer than three cell diameters (50 microns or longer) were counted as neuronal. The specification does teach on page 31, lines 13-16 that a "small percentage (around 5%) of cells also express GFAP. This is an indication that transdifferentiated cells acquire characteristics of astroglial cells, either directly or indirectly." The specification does not assess all of the potential combinations of neurogenic factors and antisense as specifically claimed. The specification does not characterize treated cells for their ability to express O4, one of the specifically claimed embodiments of the claims. The specification does not asses the full character of Neuronal cells, for example, as to whether the cells maintain features of epidermal cells and if they have multiple features of neuronal glial cells and whether they function in a manner similar to any particular types of neuronal glial cells.

The specification sets forth uses for the cells made by the claimed methods including for use as replacement tissue in gene therapy, for use to identify other neuronal growth factors and for use in assessing the effects of potential neuronal drugs.

These uses set forth by the specification would all require cells that are functionally very similar to fully differentiated and developed neuronal cells. Cells with maintain features of epidermal cells or only express a neuronal marker are not useful for any of the purposes set forth in the specification. Therefore, to be enabled, the methods claimed would need to provide a functional glial cell, useful for the uses set forth in the specification.

The filed of transdifferentiation recognized that characterization of neuronal cells based only on one marker, or neurite development would not be sufficient to reliably assess a cell as neuronal (see for example, Svendsen et al.) Additionally, the specification states that 5% of cells treated by the claimed methods expressed GFAP, relying on this marker to demonstrate transdifferentiation, however, the art recognized that a certain populations of epidermal cells already express GFAP (see for example, Kutzner et al., page 348, second column or Smith et al. page 28, first column). The results presented in the examples do not appear to reliably demonstrate that the combinations of antisense and neurogenic transcription factors tested provided cells with the features claimed, or with the features of a glial cell, as required to use these cells for the purposes set forth in the specification.

The specification only teaches in Table 1 a defined set of cells having some characteristic of a differentiated neuronal cell, the structure of which is not adequately described therein, and would not appear to have the instantly claimed features of a glial cell. As as discussed in the prior Office action, glial cell differentiation and development is a very complex process, and it is unclear that the examples described in the specification actually support that this complex process has occurred, to provide viable glial cells. For example, the textbook entitled "The Functional Roles of Glial Cells in Health and Disease", vol. 468 from the Advances in Experimental Medicine and

Biology series, Ed. By Rebecca Matsas and Marco Tsacopoulos, Kluwer Academic/Plenum Publishers, New York, NY, 1999, teaches the following about glial cells in the preface: "Glial cells outnumber neurons and make up about one-half of the bulk of the nervous system. They are divided into two major classes: first, the macroglia, which include astrocytes and oligodendrocytes in the central nervous system, and the Schwann cells in the peripheral nervous system; and second, the microglial cells. These different classes of glial cells have different functions and contribute in different ways in the development, function, and the pathology of the nervous system." The complexity of glial cell development, the discovered components of cell differentiation and development, and cell survival as a functioning glial cells are reviewed in chapter 1, Jessen et al., pages 3-10. It is stated on page 4, line 5, that "[l]ittle is known about the mechanisms that regulate the entry of crest cells to the glial lineage. One of the difficulties in studying this first step in PNS glial development has been the lack of a glial differentiation marker that defines an early lineage entry." They further state on page 4 that "[o]ne of the most notable features of the precursor cell is its acute dependence on axonal survival signals." On page 6, they state that "A striking feature of the Schwann cell phenotype is how unstable it is. If a nerve is an adult animal is transected, the myelinating and non-myelinating cells in the distal stump will promptly undergo radical lacerations in morphology and gene expression. The eventual outcome is the generation of an apparently single population of cells that show a state of differentiation comparable to that of immature cells prior to the formation of myelinating an non-myelinating cells....this process involves the dedifferentiation or development regression of individual Schwann cells and myelin break-down." These teachings provide the complexity in the art for the types of glial cells, their functions, and their carefully regulated cell phenotypes.

While the textbook, Developmental Biology, 5th Ed. , Scott F. Gilbert, Sinauer Associates, Inc. Pub., Sunderland, Mass., 1997, pages 297-299, taught in Figure 7.42, the "Hypothetical lineage restriction in the cells of the quail cephalic neural crest", the potential for glial cell development to take many different paths is clear. Neither the prior art nor the specification as filed taught the clearly delineated pathology of development of any type of glial cell from epidermal basal cells. "

The level of unpredictability in the field of development of glial cells from epidermal basal cells was high. Transdifferentiation of cells from differentiated cells was not considered to be predictable and, even post filing the state of the art was that complete transdifferentiation adult cells had not been achieved. For example, Hakelien et al. discuss the state of the art and indicate that in 2002 reports of partial transdifferentiation have been made (see p 379, second column for example) and "despite the excitement resulting from the transdifferentiation potential of adult stem cells, some controversy remains on the plasticity of these cells" (see page 380, first column, last paragraph).

To practice the methods of transdifferentiation , as claimed, to produce a glial cell with features useful to the skilled artisan, for use as set forth by the specification for gene therapy applications, drug screening or in the determination of neuronal growth factors, the skilled artisan would need to determine which, if any, of the particular combinations of antisense and neurogenic growth factors can produce a cell with features of a glial cell, as would be required, and whether or not these cells were actually differentiated and developed or if they retain features of epidermal cells. The complexity of glial cell development would suggest that other factors and further steps would be required to achieve this development. Since the specification give no guidance on how to achieve this development, and the art also had not achieved more

than partial transdifferentiation, the skilled artisan would need to determine how to proceed de novo, through undue, trial and error experimentation. Given the unpredictable nature of transdifferentiation of adult cells, it is unclear that even through such undue experimentation the skilled artisan would even be able to successfully practice the transdifferentiation methods, as claimed, to result in a cell population useful for the purposes set forth by the specification.

Response to Arguments

In response to the rejection of record under 35 USC 112, first paragraph, as lacking enablement, Applicant argues that the amendment to limit the claims to using "primary" epidermal basal cells overcomes the rejection, however, this argument does not seem relevant and is not sufficient to overcome the new rejection set forth herein under 35 USC 112, first paragraph.

Conclusion

Claims 1, 2, 5, 8, 11, 12, 16 and 22-46 are free of the prior art since the prior art did not teach nor fairly suggest the claimed step of use of antisense to MSX1 and HES1 found in each of the instant method and composition claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (571) 272-0759. The examiner can normally be reached on Monday-Thursday 6:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone

number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Lacourciere
February 9, 2004